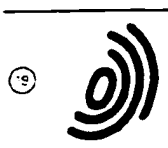


BE



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



Publication number: **0 482 498 A3**

(12)

## EUROPEAN PATENT APPLICATION

(21) Application number: **91117658.4**

(22) Date of filing: **16.10.91**

(51) Int. Cl.<sup>5</sup>: **A61K 31/66, A61K 37/64,  
A61K 31/675, A61K 31/22,  
A61K 31/215, A61K 31/19,  
A61K 31/10, A61K 31/785,  
A61K 31/455, A61K 31/195,  
A61K 31/365**

(30) Priority: **19.10.90 US 599959**

(42) Date of publication of application:  
**29.04.92 Bulletin 92/18**

(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

(88) Date of deferred publication of the search report:  
**20.10.93 Bulletin 93/42**

(71) Applicant: **E.R. SQUIBB & SONS, INC.**  
**P.O.Box 4000**  
**Princeton New Jersey 08543-4000(US)**

(72) Inventor: **Pan, Henry Y.**  
**Huntington Drive 7**  
**Princeton Jct. NJ 08550(UA)**  
Inventor: **Bergman, Michael**  
**1010 Blue Spring Road**  
**Princeton, NJ 08540(US)**

(74) Representative: **Josif, Albert, Dr.-Ing. et al**  
**Baaderstrasse 3**  
**D-80469 München (DE)**

(54) **Method for preventing diabetic complications employing a cholesterol lowering drug alone or in combination with an ace inhibitor.**

(57) A method is provided for preventing diabetes and preventing complications resulting from diabetes by administering to a diabetic patient a cholesterol lowering drug, such as pravastatin, alone or in combination with an ACE inhibitor, such as captopril, zofenopril, ceronapril, fosinopril, enalapril or lisinopril.

EP 0 482 498 A3



European Patent  
Office

## PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention  
shall be considered, for the purposes of subsequent  
proceedings, as the European search report

Application Number

EP 91 11 7658

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
X	EP-A-0 272 778 (GLAXO GROUP LTD) 29 June 1988	1	A 61 K 31/66
Y	* page 3 *	2-4, 6-8 , 11-31	A 61 K 37/64 A 61 K 31/675 A 61 K 31/22 A 61 K 31/215 A 61 K 31/19 A 61 K 31/10 A 61 K 31/785 A 61 K 31/455 A 61 K 31/195 A 61 K 31/365
X	DE-A-2 716 374 (INVESTIGACION TECNICA Y APLICADA S.A.) 3 November 1977	1	
Y	* page 8; page 11 *	2-4, 6-8 , 11-31	
P, X	EP-A-0 414 023 (FUJISAWA PHARM. CO.) 27 February 1991	1, 2	
Y	* page 3 *	3, 4, 6-8 , 11-31	
	--- -/-		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
			A 61 K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely : Claims searched incompletely : Claims not searched : Reason for the limitation of the search:</p> <p>see sheet -C-</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		29-04-1993	KRAUTBAUER B
CATEGORY OF CITED DOCUMENTS			
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			



European Patent  
Office

### CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

see sheet -B-

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,

namely claims: mentioned in item 1.



European Patent  
Office

# PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 91 11 7658

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	JPN. J. MED. vol. 29, no. 2, March 1990, pages 156 - 163 T. SASAKI ET AL. 'AMELIORATION OF PROTEINURIA WITH PRAVASTATIN IN HYPERCHOLESTEROLEMIC PATIENTS WITH DIABETES MELLITUS'	1-3, 11	
Y	* abstract; page 156; page 160 - page 162 *	4, 6-8, 12-31	
X	THE AMERICAN JOURNAL OF CARDIOLOGY vol. 66, no. 8, 18 September 1990, pages 16B - 21B R. GOLDBERG ET AL. 'COMPARISON OF THE EFFECTS OF LOVASTATIN AND GEMFIBROZIL ON LIPIDS AND GLUCOSE CONTROL IN NON-INSULIN-DEPENDENT DIABETES MELLITUS'	1-3	
Y	* page 16B; page 20B - page 21B *	4, 6-8, 11-31	TECHNICAL FIELDS SEARCHED (Int. Cl. 5)
X	ATHEROSCLEROSIS vol. 75, no. 1, 1989, pages 67 - 72 G. YOSHINO ET AL. 'LONG-TERM TREATMENT OF HYPERCHOLESTEROLEMIC NON-INSULIN DEPENDENT DIABETICS (NIDDM) WITH PRAVASTATIN (CS-514)'	1-3	
Y	* the whole document *	6-8, 11-31	
Y	DATABASE WPIL Week 8620, Derwent Publications Ltd., London, GB; AN 86-127658 & JP-A-61 064 701 (MEITO SANGYO KK) 3 April 1986 * abstract *	1, 2-4, 6-8, 11-31	
Y	G. THEWS ET AL. 'ANATOMIE PHYSIOLOGIE PATHOPHYSIOLOGIE DES MENSCHEN' 1982, WISSENSCHAFTL. VERLAGSGESELLSCHAFT MBH, STUTTGART * page 655 - page 657 *	1, 2-4, 6-8, 11-31	
	-/-		

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	WIENER MEDIZINISCHE WOCHENSCHRIFT vol. 139, no. S105, 1989, pages 9 - 17 G. BIESENBACH 'FETTSTOFFWECHSELSTÖRUNGEN BEI DIABETES MELLITUS' * the whole document *	1,2-4,6 -8,11-31	
Y	EP-A-0 000 124 (THERA) 10 January 1979 * claims 1-4 *	12-31	
Y	EP-A-0 331 014 (THERA) 6 September 1989 * column 1; claim 1 *	12-31	
Y	EP-A-0 363 671 (F. HOFFMANN-LA ROCHE AG) 18 April 1990 -----	12-31	TECHNICAL FIELDS SEARCHED (Int. Cl. 5)



European Patent  
Office

EP 91 11 7658 -B-

#### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

The problem the application tries to solve is to prevent diabetes or to prevent or reduce the risk of complications resulting from diabetes.

The proposed solution is to use cholesterol lowering drugs.

Documents nos. 1 and 2 cited in the Search Report describe the use of cholesterol lowering drugs for the wanted effect.

Therefor the general idea of using cholesterol lowering drug for preventing diabetes or diabetic complications is not new and in view of the state of the art the problem has to be redefined as finding further lipid lowering drugs for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes.

The proposed compounds are structurally and concerning their mode of action not so related as to form a single inventive concept.

There is NON-UNITY A POSTERIORI

1. Claims 1,12-15,17,19,21,23,26,29 (partially)  
2-4,6-8,11,16,18,20,22,24,25,27,28,30,31 (completely)

Use of a HMG CoA reductase inhibitor alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

2. Claims 1,12-15,17,19,21,23,26,29 (partially)  
5 (completely)

Use of a squalene synthetase inhibitor alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes



#### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

3. Claims 1,10,12-15,17,19,21,23,26,29 (partially)  
9 (completely)

Use of a fibric acid derivative (gemfibrozil, fenofibrate, clofibrate, bezafibrate, ciprofibrate, clinofibrate) alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

4. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of probucol alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

5. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of dextrothyroxine and its sodium salt alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

6. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of Bile acid sequestrants (cholestyramine, colestipol) alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

7. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of nicotinic acid alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

8. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of neomycin alone or in combination with an ACE inhibitor for manufacturing a medicament for preventing diabetes or preventing or reducing the risk of complications resulting from diabetes

9. Claims 1,10,12-15,17,19,21,23,26,29 (partially)

Use of salicylic acid derivatives (p-amino-salicylic acid, acetylsalicylic acid) alone or in combination with an ACE inhibitor for manufacturing a



European Patent  
Office

EP 91 11 7658 -3-

#### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

medicament for preventing diabetes or preventing or  
reducing the risk of complications resulting from diabetes





EP 91 11 7658

-C-

A compound cannot be defined by its activity (e.g. cholesterol lowering, HMG CoA reductase inhibiting, ACE-inhibiting etc.)

This characterization as well as descriptions of substances as analogs or derivatives of other compounds and the use of huge Markush formulas does not make clear which substances are meant.

The search therefor had to be restricted to the compounds which are explicitly mentioned in the claims and the general inventive idea.

Please note that this restriction is also valid for possible further search for the subjects not searched now because of non-unity. (see sheet B).  
(Art. 84 EPC)